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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/581,005	06/06/2000	CHRISTOPH VON EICHEL-STREIBER	113.1007	2246

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DAVIDSON, DAVIDSON & KAPPEL, LLC
485 SEVENTH AVENUE, 14TH FLOOR
NEW YORK, NY 10018

EXAMINER	
PARAS JR, PETER	

ART UNIT	PAPER NUMBER
1632	10

DATE MAILED: 01/03/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/581,005	Applicant(s) VON EICHEL-STREIBER ET AL.	
	Examiner Peter Paras	Art Unit 1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 23-51 is/are pending in the application.

4a) Of the above claim(s) 35-51 is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 23-34 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group I, claims 23-34, in Paper No. 9 is acknowledged. The traversal is on the ground(s) that the Cossart reference does not teach the inventive concept of the claimed invention as required under PCT Rule 13.1. Applicants argue that Cossart teaches a different inventive concept, particularly because the foreign DNA remains under control of the bacteria and not under the control of the eukaryotic cells in accordance with the instant invention This is not found persuasive because the instant claims, particularly claim 23 does not recite that the foreign DNA is exclusively under eukaryotic control. As such Cossart has been properly applied.

The requirement is still deemed proper and is therefore made FINAL.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 23-34 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are directed to bacteria that are useful as a vehicle for gene transport and gene transfer to eukaryotic cells of an organism for inducing a targeted somatic transgenesis in cells, tissues or organs, except the germ-line cells of the organism, wherein the bacteria comprise a foreign DNA integrated into an episomal vector.

The specification has taught bacteria that can be used to transfer heterologous nucleotide sequences into eukaryotic cell lines. The specification has not taught transfer and expression of heterologous nucleotide sequences into the somatic cells of an organism in vivo using the claimed bacteria. Although the claims are not limited to use of the claimed bacteria to transfer heterologous nucleotide sequences into the somatic cells of an organism *in vivo*, the claims however when taken with the teachings of the specification clearly read on the use of such a vector for *in vivo* somatic cell gene transfer. The specification has failed to provide any guidance, direction, or working examples that demonstrate *in vivo* somatic cell gene transfer using the claimed bacteria. The specification , rather has only contemplated that the claimed bacteria can be used for such purposes and has failed to provide evidence of a single organism whose somatic cells comprise foreign nucleotide sequences delivered *in vivo* by the claimed bacteria. Given the lack of guidance or direction provided by the instant specification into would have required undue experimentation to use the claimed bacteria for *in vivo* somatic cell gene transfer as is consistent with the teachings of the instant specification.

The claims are directed to bacteria that can be used to transfer heterologous nucleotide sequences into the somatic cells of an organism in vivo. Although the specification has failed to provide guidance or working examples that teach how to use the claimed bacteria for *in vivo* somatic cell gene transfer, the skilled artisan cannot rely on the state of the art for teachings that demonstrate the use of the claimed bacteria for *in vivo* somatic cell gene transfer. This is because the state of the art is unpredictable with respect to use of bacteria as vehicles for *in vivo* somatic cell gene transfer. In particular, it is unpredictable if any such heterologous nucleotide sequences can be expressed in somatic cells of an organism *in vivo* at a level sufficient to result in a phenotypic effect. For bacteria to function as DNA delivery systems into mammalian cells , the bacteria must first enter the cell and then escape from the vacuole to the cytosol. Movement from the vacuole to the cytosol is unpredictable because in many instances the bacteria are lysed by the host cell's defense system and any plasmids carried by the bacteria are degraded preventing expression of heterologous nucleotide sequences. At best it would appear that only a few cells, if any may be transformed with plasmid DNA carried by a bacterial vehicle as Grillot-Courvalin (Nature Biotechnology, 1998, 16: 862-866) suggest that "direct introduction of DNA from bacteria to mammalian cells has been reported in very few instances". See page 865, starting with the first line of the discussion. Grillot-Courvalin support such observations by reporting that "factors such as entry route may have an effect" on DNA delivery. Grillot-Courvalin go on to report that a mouse dendritic cell line, which can internalize bacteria via micropinocytosis, did not express incoming DNA at 24 hours post-transfer.

Grillot-Courvalin suggest that this failure could reflect rapid degradation of the invading bacteria by this cell type. It would appear that use of bacteria as DNA delivery vehicles is not very efficient in other cell lines as well as Grillot-Courvalin have reported that *E.coli* carrying a nucleotide sequence encoding the green fluorescent protein are only able to transform 0.3-1% of a transfected macrophage cell line. See the paragraph bridging pages 864-865. These observations are corroborated by Dietrich et al (Nature Biotechnology, 1998, 16: 181-185) who report that only about 0.03% of macrophages infected with a mutated form of *Listeria monocytogenes* express a green fluorescent protein reporter gene. See page 183, column 2. Dietrich et al also suggest that expression of a heterologous nucleotide sequence is not stable over time by observing a gradual loss of fluorescence over time. See page 183 at the bottom of column 2. Dietrich report that the low efficiency of expression of GFP as compared to the number of macrophages infected may be due to the fact that "only some of the attenuated bacteria infecting the host cells survive the antimicrobial milieu inside the phagosome and are able to escape into the host cell cytosol, whereas the others are totally digested, including the plasmid DNA and that not all listeriae being taken up reach the host cell cytosol as an intact viable entity, but the plasmid DNA is still released into this compartment. See page 184 at the top of column 2.

If the intended use for such a bacterial vector is as an oral vaccine to deliver an antigen to muscosal tissues the issues of unpredictability regarding antigen stability and antigen expression at a level sufficient to induce an immune response abound. A general issue of unpredictability of oral vaccines is the poor immunogenicity displayed

by most antigens when given orally. See Pascual et al (Behring Inst. Mitt., 1997, 98: 143-152) on page 143. Pascual et al report that there are several issues compounding the development of live oral bacterial vaccine vectors, including the fact that there is a "lack of a well tolerated, highly immunogenic bacterial vector for use in humans". See page 144. Pascual et al go on to suggest that the folding of antigens in the bacterial cytoplasm can affect humoral immunity to discontinuous epitopes such that misfolded antigens expressed by bacterial vectors would be expected to induce humoral immunity only against continuous epitopes and irrelevant discontinuous epitopes; such is a significant limitation of bacterial vaccine vectors. See page 145.

The state of the art as evidenced above suggests that use of bacteria as a vehicle for transferring heterologous nucleotide sequences to eukaryotic cells of an organism is undeveloped, inefficient, and unpredictable. The studies recited above demonstrate that only low efficiency of reporter gene expression occurs in cell lines *in vitro* and only contemplate that bacteria could be used to transfer heterologous DNA sequences to the somatic cells of an organism supporting the Examiner's assertion that use of bacteria to transfer DNA *in vivo* is undeveloped and unpredictable.

Given, the unpredictable and undeveloped nature of the state of the art, the lack of working examples provided by the specification it would have required undue experimentation to make and use the claimed bacteria as vehicles for transferring heterologous DNA to the eukaryotic cells of an organism *in vivo* without a reasonable expectation of success.

Claims 31-33 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The invention appears to employ novel strains of *Listeria monocytogenes*. Since the *Listeria* strains are essential to the claimed invention they must be obtainable by a repeatable method set forth in the specification or otherwise be readily available to the public. If the claimed *Listeria* strains are not so obtainable or available, the requirements of 35 USC 112 may be satisfied by a deposit of the EBV. 37 CFR 1.802. The specification does not disclose a repeatable process to obtain the claimed *Listeria* strains and it is not apparent if the claimed *Listeria* strains are readily available to the public. Thus, a deposit is required for enablement purpose. If the deposit is made under the terms of the Budapest Treaty, then an affidavit or declaration by applicants, or a statement by an attorney of record over his or her signature and registration number, stating that the specific strain has been deposited under the Budapest Treaty and that the strain will be irrevocably and without restriction or condition released to the public upon the issuance of a patent, would satisfy the deposit requirement made herein. 37 CFR 1.808

If the deposit has not been made under the Budapest Treaty, then in order to certify that the deposit meets the criteria set forth in 37 CFR 1.808, applicants may provide assurance of compliance by an affidavit or declaration, or by a statement by an attorney of record over his or her signature and registration number, showing that

(a) during the pendency of this application, access to the invention will be afforded to the Commissioner upon request;

(b) all restrictions upon availability to the public will be irrevocably removed upon granting of the patent;

(c) the deposit will be maintained in a public depository for a period of 30 years or 5 years after the last request or for the effective life of the patent, whichever is longer;

(d) a viability statement in accordance with the provisions of 37 CFR 1,807; and

(e) the deposit will be replaced if it should ever become inviable.

As required under 37 CFR 1.809(d), the specification shall contain: (1) the accession number for the deposit; (2) the date of deposit; (3) a description of the deposited biological material sufficient to identify it and to permit its examination; and (4) the name and address of the depository.

Although, the depository, DSMZ-the German collection of Microorganisms and Cell Cultures, used by Applicants is recognized by the MPEP 2405-8, Applicants have not complied with one or more of the requirements of the Budapest Treaty, 37 C.F.R. 1.801-1.809. Compliance is required.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Peter Paras, Jr., whose telephone number is 703-308-8340. The examiner can normally be reached Monday-Friday from 8:30 to 4:30 (Eastern time).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Crouch, can be reached at 703-308-1126. Papers related to this application may be submitted by facsimile transmission. Papers should be faxed via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center numbers are (703) 308-4242 and (703) 305-3014.

Inquiries of a general nature or relating to the status of the application should be directed to Kay Pinkney whose telephone number is (703) 305-3553.

Peter Paras, Jr.

Art Unit 1632

Deborah Crouch

DEBORAH CROUCH
PRIMARY EXAMINER
GROUP ~~1800~~ 1630